Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-4, 6, 8-9, 14-17, 22-23, 25-26, 36 and 38 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventor had possession of the claimed invention for the reasons of record set forth in the Office Action mailed August 2, 2001. The Office Action states that "Applicant's arguments filed 25 February 2002 have been fully considered but they are not persuasive."

Specifically, the Office Action states that "[t]he claimed biologically active mutants, fragments, derivatives or fusion proteins of restin have not been adequately described in the specification such that one of skill in the art would reasonably conclude that Applicant was in possession of such a broad genus of compounds at the time the invention was made."

Applicant notes that all of the rejections within the Office Action are written as though the claims are genus/species claims. However, all of the claims currently under examination are methods claims. No compositions of matter are being claimed. The Office Action provides no reasoning as to why Applicant is being requested to provide support for additional species. Applicant therefore respectfully requests that the claims be passed to issue, as no arguments have been advanced suggesting that the methods are not fully described and enabled.

Applicant has amended the claims to recite methods of producing biologically active anti-angiogenic proteins of restin or biologically active anti-angiogenic mutants, fragments and fusion proteins of restin. Applicant respectfully submits that those of ordinary skill in the art are well-versed in the isolation of such mutants, fragments and fusion proteins.

Applicant has also amended the claims to recite methods of making "biologically active anti-angiogenic" restin and its "biologically active anti-angiogenic" mutants, fragments and fusion proteins by inserting an isolated polynucleotide sequence encoding "biologically active anti-angiogenic" restin or a "biologically active anti-angiogenic" mutant, fragment or fusion protein thereof into a yeast expression vector.

The Office Action notes that Applicant has disclosed the restin protein, which is 181 amino acids long, and also apomigren, which comprises about the last 85 amino acids of the restin protein. Both restin and apomigren are demonstrated to have anti-angiogenic properties.

The Office Action then states that "[a]lthough Applicant has adequately described apomigren and possibly fragments comprising the 85 amino acids of apomigren, the claims read on sequences that include the first 97 amino acids of restin."

Applicant is unclear if the Office Action intends to say that the claims read on sequences of, *e.g.*, amino acids 1-96, or that the claims read on sequences of more than 85 amino acids, that include apomigren.

If the Office Action intends the first, then the claims as written are clear on their face, since one of ordinary skill in the art would readily understand that a fragment of restin comprising for instance, amino acids 1-50, is less likely to possess anti-angiogenic properties than a fragment comprising all or a part of apomigren. More importantly, any mutant, fragment or fusion protein of restin not possessing anti-angiogenic properties would automatically fall outside the scope of the present claims, since the claims as amended recite methods of producing "a biologically active anti-angiogenic restin" or a "biologically active anti-angiogenic mutant, fragment or fusion protein thereof". Anti-angiogenic properties are a requirement for a restin protein or mutant, fragment or fusion protein thereof to fall within the scope of the claims. The claims therefore read on sequences that include the first 97 amino acids of restin only if these sequences are anti-angiogenic.

Alternatively, it may be that the Office Action means that the claims read on sequences that are shorter than restin, but contain the amino acids that make up apomigren (amino acids 97-181). If so, then the scope of the claims is also clear, for the same reasons as given above. The claims as amended recite methods of producing anti-angiogenic proteins, and mutants, fragments and fusion proteins thereof, therefore, proteins, mutants, fragments and fusion proteins not possessing this activity lie outside the scope of the claims.

The Office Action states on page 5 that "it should be noted that the scope of the claims is well beyond the scope of apomigren." Applicant has amended the claims to recite methods of

making "biologically active anti-angiogenic" restin protein or its "biologically active anti-angiogenic" mutants, fragments and fusion proteins by inserting an isolated polynucleotide sequence encoding "biologically active anti-angiogenic" restin or a "biologically active anti-angiogenic" mutant, fragment or fusion protein of restin. Proteins, mutants, fragments and fusion proteins which are not biologically active and/or which are not anti-angiogenic clearly lie outside the scope of the claims. It is therefore unclear how the scope of the claims can be interpreted to be "well beyond" the scope of apomigren.

On page 5 of the Office Action, it is stated that Applicant has not described functional fragments of the approximately 85 amino acids of apomigren, and that "Applicant has done little more than disclose apomigren and send the skilled artisan on a hunt for mutants, fragments . . . or fusion proteins of apomigren having anti-angiogenic activity." The Office Action quotes the Manual of Patent Examining Procedure (M.P.E.P.) § 2163 (I)(A) to support this contention.

However, this very section of the M.P.E.P. also states that "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art" (emphasis added).

Applicant respectfully submits that, according to the requirements of the M.P.E.P., the subject matter of the present claims is adequately described in the specification. The claims do not require any essential or critical features which are not adequately described in the specification, and are not either conventional in the art or already known to one of ordinary skill. The overall restin protein sequence (SEQ ID NO:10) has been provided, along with the information and a demonstration that shorter sequences can be made which possess the same properties as the overall sequence. Making proteins of predetermined lengths from a known nucleic acid sequence is conventional, and can be done by persons of moderate skill in the art, as are methods for making amino acid substitutions, and fusion proteins. Testing the resulting protein sequences for anti-angiogenic activity is straightforward, and easily done according to methods well-known in the field, and which are also provided in the specification. One of ordinary skill, reading the specification, is therefore placed in possession of all information

needed to make and use anti-angiogenic restin protein and its anti-angiogenic mutants, fragments and fusion proteins.

The Office Action also states that because the Reply to the previous Office Action stated that the "activity is somewhere within the region making up the apomigren sequence", Applicant is somehow admitting that "no known correlation" exists between the fragments and the anti-angiogenic activity. This is flatly untrue. The restin protein is anti-angiogenic. Apomigren, which makes up the C-terminal 85 amino acids of restin, is also anti-angiogenic. This demonstration that restin's anti-angiogenic activity resides within a subset of the overall amino acid sequence IS the correlation between fragments of restin and the anti-angiogenic activity.

The Office Action cites several cases to support the rejection on written description grounds, including *Vas-Cath Inc. v. Mahurkar* (935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991)), *Lockwood v. American Airlines, Inc.* (107 F.3d 1565, 41 U.S.P.Q.2d 1961 (Fed. Cir. 1997)), and *Regents of the University of California v. Eli Lilly & Co.* (119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997); "*University of California*").

In *Vas-Cath*, the question on appeal was whether or not the drawings in Mahurkar's design patent, which had no textual description, adequately met the written description requirement and supported the claims of a utility application claiming priority to the design patent. The District Court had held that they did not, stating that the drawings were not capable of stating what the invention was and could not describe what was novel or important about the invention. The Federal Circuit held that this was in error, and noted that Mahurkar had patented what the drawing showed, stating that

> "Although [the applicant] does not have to describe exactly the subject matter claimed,... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (citations omitted). "[T]he test for sufficiency of support in a parent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'" *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985)

> (*quoting In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

(*Id.* at 1116). *Vas-Cath* therefore shows that an application with much less description than is provided in the present application, may nevertheless satisfy the written description requirement.

In *Lockwood*, the patentholder unsuccessfully argued that claims to an interactive sales system that included (I) a computer system connected to multiple vendors and (II) merchandising apparatus containing video disk players, were supported by a parent application that disclosed (i) a single computer terminal, and (ii) a central computer with a video disk player. Applicant's representative has been unable to find either legal arguments or facts within this opinion that are applicable to the present claims.

The situation in *University of California* reflects a genus-species problem. In that case, the court found the claims of U.S. Patent No. 4,652,525, drawn to DNA encoding vertebrate, mammalian or human insulin, to be invalid for lack of an adequate written description of the claimed subject matter. The patent owned by the University of California disclosed a cDNA encoding rat insulin and a prophetic example teaching a method for isolating a cDNA encoding human insulin, but claimed genes encoding mammalian insulin generally. The disclosure did not include a description of the characteristics of any cDNAs encoding insulin other than rat insulin. The court held that a description of rat insulin cDNA is not a description of the broad class of vertebrate or mammalian cDNA, and quoted *Fiers v. Sugano* (984 F.2d 1164, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993)) in stating that a "written description of an invention involving a chemical genus . . . 'requires a precise definition, *such as by structure, formula, **[or]** chemical name*" (*University of California*, at 1405, emphasis added). The Court expanded on this, stating that

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus **OR** of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

(*Id.* at 1406, emphasis added). The Court then quoted *In re Grimme*, 274 F.2d 949, 952, 124 U.S.P.Q. 499, 501 (C.C.P.A. 1960), and stated that "it has been consistently held that the naming

of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.' We will not speculate in what other ways a broad genus of genetic material may be properly described . . . ." (*Id.* at 1406, emphasis added). The court clearly did not overrule cases such as *In re Angstadt and Griffin*, 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976), but left the door open to other methods of providing a unifying description of a genus of genetic material, as long as those methods do not contradict long-established law on the subject.

The Court then described how the University of California's disclosure failed to provide adequate written description:

> a generic statement such as . . . 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because *it does not distinguish the claimed genus from others*, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.

(*Id.* at 1406, emphasis added). Specifically, the University was denied its claims to mammalian sequences because it had not properly defined that genus. That is, if one of ordinary skill were to isolate an insulin gene from a bird, he would have no way to know if that gene also happened to be represented amongst the family of mammalian insulins, and therefore came within the scope of the claims. In order to determine if he were inadvertently infringing, he would have to isolate *all* mammalian insulin genes (except rat) and compare them to his bird insulin gene, because the University of California inventors had provided no way for one to know if a newly-isolated sequence came within the scope of their claims. Put another way, it would have required undue experimentation for one to determine if newly isolated subject matter came within the scope of the University's claims.

The Examiner's reliance on *University of California* is misplaced. Applicant is not claiming a genus broader than the species disclosed, as was done in *University of California*.

Instead, Applicant has disclosed the restin sequence, and are claiming the genus of sequences which (1) are fragments, *i.e.*, subsequences, of that sequence, and (2) are anti-angiogenic. Both elements are required for a fragment to fall within the scope of the claims as presently amended. Methods of making fragments of known sequences are well known in the art, and one of ordinary skill would recognize that because Applicant was in possession of the full-length sequence logically requires that he was also in possession of subsequences of this overall sequence, because such subsequences are inherent in the overall sequence. The set of total possible fragments of SEQ ID NO:10 is limited, and is easily set forth with no more than a pencil and paper. The subset of those fragments which possess anti-angiogenic activity and therefore come within the scope of the present claims is fewer, and easily determined by one of ordinary skill using the methods set forth in the specification.

The Office Action insists that "Applicant must show some common structural feature of either the apomigren sequence or the entire restin sequence that would allow one of skill in the art to visualize the broad genus claimed", and that "the written description rejection requires that Applicant at least teach regions, consensus sequences or motifs required for the anti-angiogenic activity of the sequences such that one of skill in the art would appreciate that Applicant actually invented or had possession of that which is claimed."

Applicant respectfully submits that the Office Action is requiring an level of precision that is simply not supported by either the Office, the Board, or the Courts. Applicant should not be required to disclose every possible anti-angiogenic fragment of restin, because one of ordinary skill in the art would readily understand that Applicant was in fact in possession of anti-angiogenic restin and its anti-angiogenic fragments. Applicant knows of no requirement that to be "in possession" of an invention, one must be in physical possession of the claimed subject matter. If this were true, the MPEP would not state that specifications may include prophetic examples and do not actually need to be reduced to practice prior to filing (see, *e.g.*, MPEP § 2164.02).

Applicant's specification discloses anti-angiogenic restin, and methods of producing same. The specification also discloses that the anti-angiogenic activity lies within a

subsequence, and demonstrated that this is so by disclosing anti-angiogenic apomigren. Denial of patent protection to anti-angiogenic restin mutants, fragments and fusion proteins would give free rein to copyists to take the heart of Applicant's invention by adding, deleting or substituting a single amino acid to or from the apomigren sequence, or by adding another known protein (*e.g.*, endostatin) to restin to make a fusion protein.

For the above reasons, Applicant respectfully submits that the specification and claims as presently amended comply with the written description requirement of 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection on this ground be reconsidered and withdrawn.

Applicant submits that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicant respectfully requests the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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MARKED-UP VERSION OF AMENDMENTS:

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Please amend claims 1, 6, 8-9, 14, 17, 22-23, 25-26, 36 and 38 as follows:

1. (Twice Amended) A method of producing a biologically active anti-angiogenic protein, or a biologically active anti-angiogenic mutant, fragment[, derivative] or fusion protein thereof, comprising:

   (a) inserting an isolated [polynucleotide comprising a] polynucleotide sequence encoding a biologically active [an] anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof, into a yeast expression vector, wherein the vector contains a multiple cloning site; and

   (b) transforming an appropriate yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the biologically active anti-angiogenic restin protein, or the biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof;

   thereby producing a biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof.

6. (Twice Amended) The method of Claim 1 wherein the biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof is produced at a concentration of 10-20 milligrams or more per liter of culture fluid.

8. (Twice Amended) The method of Claim 1 wherein the isolated polynucleotide of step (a) additionally comprises a polynucleotide linker, and the biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof produced in step (b) additionally comprises at least one amino acid residue resulting from the polynucleotide linker.

9. (Twice Amended) The method of Claim 8 wherein the biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof produced comprises two additional amino-terminus amino acid residues.

14. (Twice Amended) The method of Claim 1 wherein the vector of step (a) comprises a pPICzαA plasmid wherein the plasmid contains a multiple cloning site, said cloning site comprising a His.Tag motif and wherein the biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof produced in step (b) comprises a histidine tag motif.

17. (Twice Amended) The method of Claim 14 wherein the biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof is produced at a concentration of 10-20 milligrams or more per liter of culture fluid.

22. (Twice Amended) A method of producing a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, fragment[, derivative] or fusion protein thereof, comprising:

(a) inserting an isolated [polynucleotide comprising a] polynucleotide sequence encoding [an] a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof, wherein the polynucleotide additionally comprises a linker, wherein the polynucleotide linker encodes at least one amino acid, into a yeast expression vector comprising a pPICzαA plasmid wherein the plasmid contains a multiple cloning site; and

(b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the biologically active anti-angiogenic restin protein or biologically active anti-angiogenic mutant, fragment or fusion protein thereof, comprising at least one amino acid residue resulting from the linker polynucleotide;

thereby producing a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof.

23. (Twice Amended) The method of Claim 22 wherein the polynucleotide additionally encodes angiostatin, endostatin, or mutants, [derivatives,] fragments or fusion proteins thereof[, or any combination thereof].

25. (Twice Amended) A method of producing a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, fragment[, derivative] or fusion protein thereof, comprising:

(a) inserting an isolated [polynucleotide comprising a] polynucleotide sequence encoding [an] a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof, wherein the polynucleotide

additionally comprises a linker[,] and wherein the polynucleotide linker encodes at least one amino acid, into a yeast expression vector comprising a pPICzαA plasmid wherein the plasmid contains a multiple cloning site and wherein the cloning site additionally comprises a histidine tag motif; and

(b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the biologically active anti-angiogenic restin protein or biologically active anti-angiogenic mutant, fragment or fusion protein thereof comprising at least one amino acid residue resulting from the linker polynucleotide, and wherein the protein or mutant, fragment or fusion protein thereof additionally comprises a histidine tag motif;

thereby producing a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof.

26. (Twice Amended) The method of Claim 25 wherein the polynucleotide additionally encodes endostatin, angiostatin, or mutants, [derivatives,] fragments or fusion proteins thereof[, or any combination thereof].

36. (Amended) A method of producing biologically active anti-angiogenic restin, or a biologically active anti-angiogenic mutant, fragment[, derivative] or fusion protein thereof, comprising:

(a) inserting an isolated [polynucleotide comprising a] polynucleotide sequence encoding a biologically active anti-angiogenic [an] restin, or a biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof, wherein the polynucleotide additionally comprises a linker, wherein the polynucleotide linker encodes at least one amino

acid, into a yeast expression vector comprising a pPICzαA plasmid wherein the plasmid contains a multiple cloning site; and

(b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the biologically active anti-angiogenic restin or biologically active anti-angiogenic mutant, fragment or fusion protein thereof, comprising at least one amino acid residue resulting from the linker polynucleotide;[,]

thereby producing a biologically active anti-angiogenic restin, or biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof.

38. (Amended) A method of producing biologically active anti-angiogenic restin, or a biologically active anti-angiogenic mutant, fragment[, derivative] or fusion protein] thereof, comprising:

(a) inserting an isolated [polynucleotide comprising a] polynucleotide sequence encoding a biologically active anti-angiogenic [an] restin, or a biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof, wherein the polynucleotide additionally comprises a linker, wherein the linker encodes at least one amino acid, into a yeast expression vector comprising a pPICzαA plasmid wherein the plasmid contains a multiple cloning site and wherein the cloning site additionally comprises a histidine tag motif; and

(b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the biologically active anti-angiogenic restin or biologically active anti-angiogenic mutant, fragment or fusion protein thereof wherein the protein or mutant, fragment or fusion protein comprises at least one amino acid residue resulting from the linker polynucleotide and a histidine tag motif;[.]

thereby producing a biologically active anti-angiogenic restin, or biologically active anti-angiogenic mutant, [derivative,] fragment or fusion protein thereof.